Remarks and Arguments

The troubled history of the present application goes back to the filing date of March 26, 2001. After the applicants were forced to make an election under a restriction requirement dated October 26, 2002, a first office action issued on December 9, 2002. In that office action, prior art rejections were made against all of the remaining claims, based in whole or in part on U.S. Patent No. 6,436,635 ("Fu"). The applicants responded by making only cosmetic changes to the claims, and argued that the application of Fu was inappropriate. A final office action was then issued on June 3, 2003 in which the examiner reasserted the earlier rejection, and stated that the applicants' arguments had been unpersuasive. The applicants responded again on October 29, 2003, without amending the claims, and attempted to explain further why the rejections based on Fu were not proper. These arguments were again rejected in an advisory action dated November 10, 2003. A Request for Continued Examination (RCE) was then filed on December 2, 2003. In a telephone interview with the examiner on December 18, 2003, the applicants were finally able to convince the examiner of the differences between Fu and the present invention and, with the entry of an examiner's amendment to Claim 1, all of the claims were allowed. However, the application was dealt another setback when, on April 21, 2004, it was withdrawn from issue, and the current office action was issued by a new examiner, citing prior art that was previously uncited.

Eighteen months later, having paid a second filing fee, the applicants now find themselves back at the beginning, with new prior art rejections facing their claims. There are now two primary references, U.S. Patent No. 5,700,642 ("Monforte '642") and U.S. Patent No. 5,830,655 ("Monforte '655"), each being cited separately under 35 U.S.C. §102(b). Monforte '642 was found to anticipate each of Claims 1-15, 23 and 25-34, while Monforte '655 was found to anticipate each of Claims 1-19, 23 and 25-34. Although the examiner must therefore have concluded that Monforte '655 includes all of the elements of Claims 1-19, 23 and 25-34, for some reason these claims are also included in an obviousness rejection under 35 U.S.C. §103(a) that relies on the combination of Monforte '655 and U.S. Patent No. 6,251,600 ("Winger"). It is not clear

why the examiner would apply the combination of Monforte '655 and Winger against claims that were determined to be anticipated by Monforte '655 alone. However, the examiner does state that "Monforte ['655]... does not specifically address RNAse H based mismatch detection methods," and appears to cite Winger in an attempt to make up for this deficiency.

Any confusion raised by the examiner's application of prior art may be rectified by the fact that none of the prior art references, whether cited alone or in combination with one another, provides any suggestion of the applicants' claimed invention. First, it should be noted that Monforte '655 is a patent that matured from an application that was a continuation-in-part of the application leading to Monforte '642, and a terminal disclaimer was apparently filed relative to the two patents. Thus, it is clear that the basic premise of both disclosures is essentially the same, and most of the relevant points regarding this prior art apply equally to both patents. The Monforte prior art is discussed in more detail below.

Both Monforte patents are directed to a method for providing modified oligonucleotide primers that have a cleavable moiety to make it easier to obtain useful sizing and sequence information regarding primer extension products. By inserting a cleavable site into the extension product, especially one close to the 3' end of the primer, the cleaved portion has a relatively large amount of new fragment information. By immobilizing the primer on a solid support, cleaving at the other end of the extension product results in a large portion of the primer fragment remaining attached to the solid support. The cleaved extension segments may thereafter be sized using mass spectrometry.

In contrast, the present invention provides an analysis method that does a special type of multiplexed amplification of nucleic acid templates in a way that allows the segregation of the different extension products. In particular, a chip is used with spatially separate locations that each contain a photocleavable oligonucleotide probe (*i.e.*, primer) covalently bound to the chip surface for a particular target sequence to be

investigated. The plurality of different primers on the chip are used to allow the analyzing of a complete set of different target sequences. All of the primers are simulataneously modified in template dependent reactions, including: primer elongation; ligation; and restriction by endonucleases. A mass spectrometric measurement is then done sequentially at each location on the chip. The spatial separation of the primers results in mass spectra with reduced complexity, because each spectrum can be associated with just one target sequence.

In discussing the Monforte '642 reference, the examiner has identified column 22, lines 25-41 and column 27, lines 3-10 as being sections of the reference that were thought to disclose multiplexed amplification of the sample of genetic material. The identified section in column 22 appears to be just a general description of PCR, and not particular to multiplexed amplification. In the section in column 27, Monforte '642 mentions multiplexing "to produce PCR products of varying sizes, with each size correlating to a unique PCR product for a specific pathogen." This method involves adding cleavable primers for each of the pathogens to the PCR reaction, so as to generate PCR products having different lengths corresponding to the different pathogens. Keeping with the general goals of the patent, the PCR products are reduced in size using cleavage so as to improve their measurability by mass spectrometry.

The multiplexing technique of Monforte '642 that is discussed above differs from the present invention in that it is intended for analyzing multiple pathogens using a single mass spectrum. The present invention uses a multiplexed amplification of the target material to produce the desired templates using non-cleavable primers. However, a chip is then used that has spatially separated photocleavable primers that function as probes, and are immobilized at the surface of the chip prior to template dependent modification. By reaction between the probes and the templates, the information under investigation is transferred from the target sequences of the templates to the probes. The reaction products may thereafter be independently

measured, such that a different spectrum is produced for each of the spatially separated probes.

With regard to the applicants' claim language regarding the use of separate immobilization regions on a chip, the examiner cites column 24, line 57 through column 25, line 3 of Monforte '642. This description is with regard to a "shotgun type" sequence analysis in which different primers are immobilized at different locations on a sample support. A sample with an unknown sequence is then reacted with the primers on the support, such that extension products will form only where complementary sequences exist. This may allow for identification of the unknown material but, obviously, uses just a single nucleic acid template. In contrast, the present invention uses different primers immobilized at separate locations on a support to hybridize to a plurality of known target sequences.

With regard to the Monforte '655 patent, many of the examiner's references are the same as with Monforte '642. For example, column 38, lines 42-55 is the same as column 24, lines 57-67, and is therefore distinguishable from the present invention for the same reasons. Indeed, both Monforte references lack all of the features of the applicants' claimed invention.

In an attempt to clarify the language of Claim 1 without narrowing its scope, Claim 1 has been amended to point out that the probes at the spatially separated locations are each for a different one of the target sequences to be investigated. As amended, Claim 1 recites a method for the analysis of a sample of genetic material that includes the steps of producing an amount of the sample of the genetic material using multiplexed amplification, and using a chip having spatially separated locations each containing a photocleavable oligonucleotide probe for a different one of the target sequences to be investigated. Using the templates produced in the amplification step, all of the probes on the chip are modified synchronously in a template dependent manner, so that the information is transferred from the target sequences of the

templates to the probes. The probes are then separated from the templates, and are cleaved and mass spectrometrically measured.

As discussed above, by spatially separating the probes for the different target sequences, a different product results at each location. This, in turn, allows independent handling of the different sites, so that each may be measured in its own mass spectrum. This is significantly different than anything suggested by the Monforte patents, including the embodiment in which individual probes of Monforte are immobilized at different sites on a support for the purposes of a "shotgun type" analysis, that is, where a sample with an unknown sequence is applied to the different probes in an attempt to identify it based on the probe to which it hybridizes. Each of claims 2-34 depends ultimately from Claim 1, and each of these claims is likewise undisclosed and unsuggested by either of the Monforte patents. As such, reconsideration of Claims 1-15, 23 and 25-34 under the rejection based on Monforte '642 is respectfully requested. Similarly, reconsideration of Claims 1-19, 23 and 25-34 under the rejection based on Monforte '655 is also respectfully requested.

With regard to the rejection of Claims 1-34 under 35 U.S.C. §103(a), it is unclear why the Winger reference would be applied in combination with Monforte '655 to reject claims that were thought to be anticipated by Monforte '655 alone. Nevertheless, the application of the Monforte '655 and Winger combination will be addressed. In making this rejection, the examiner correlates each of the limitations of the applicants' Claim 1 with some part of the Monforte '655 reference. In fact, these correlations are just reproduced verbatim from the earlier application of Monforte '655 under 35 U.S.C. §102(b). Winger is apparently not used in the application of the prior art against Claim 1. Discussion of Winger does not come until later in the examiner's analysis, where it is stated that "Monforte, while teaching restriction endonuclease cleavage methods, and suggesting the use of RNAse based methods, as discussed above, does not specifically address RNAse H based mismatch detection methods." Based on the examiner's analysis, it appears that the Winger reference is relevant only to Claim 22, which mentions the use of RNase.

Winger discloses methods of homogeneous nucleotide amplification and, in column 4, lines 48-50, mentions the use of RNase H for a cleavage function. Winger, however, seems otherwise unrelated to the present invention. Thus, the prior art combination of Monforte '655 and Winger seems no more suggestive of the applicant's claimed invention than Monforte '655 alone. There is no suggestion in this prior art combination of any of the rejected claims, for the same reasons as provided above with regard to the examiner's rejections under 35 U.S.C. §102(b). Reconsideration of Claims 1-34 under the examiner's obviousness rejection is therefore respectfully requested.

The examiner's indefiniteness rejection of Claim 24 under 35 U.S.C. §112, second paragraph, has been addressed herein by amending Claim 24 to remove the word "the" from the term "the ribonucleotides." As this is believed to obviate any lack of antecedent basis, reconsideration of Claim 24 under this ground for rejection is respectfully requested.

In light of the foregoing amendments and remarks, it is respectfully requested that all the claims be allowed such that the application may be passed to issue. If it is believed that a telephone conference would help expedite prosecution of the application, the examiner is encouraged to call the undersigned. The Commissioner is hereby authorized to charge any fees due for the filing of this paper to the applicants' attorneys' Deposit Account No. 02-3038.

Respectfully submitted

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